## REMARKS

Claims 1-35 are currently pending in the application. Applicants respectfully request reconsideration and allowance of the claims currently pending in the application.

Applicants' representative filed a Revocation and Power of Attorney with Statement Under 37 C.F.R. § 3.73 (b) on April 9, 2003. To date, Applicants have not received any notification of acceptance of power of attorney. The Official Actions mailed October 3, 2003 and March 23, 2004 were sent to Applicants' previous representative. Copies of relevant documents regarding this matter and the return post card having a Patent and Trademark Office date stamp of April 17, 2003 were submitted with the response filed January 5, 2004. Applicants respectfully reiterate the request that the Office records be updated.

I. Rejections based on 35 U.S.C. §102 and § 103

In the final Office Action, the Examiner states that "stimulation compound" is not defined in the specification in such a way to exclude the compounds taught in the prior art. The Examiner is mischaracterizing the claim limitation. Claim 1 states "a stimulation compound that stimulates the production of VEGF" (or growth factor in claim 31). This clause by itself distinguishes over the references, none of which disclose or teach stimulating the production of growth factors. The Carlyle and Martin references teach, for example, VEGF or a VEGF agonist to produce endothelial cells, not to stimulate VEGF or growth factors. The Keogh and Slaikeu references teach, for example, biomolecules having a 1,2 dicarbonyl moiety for covalently bonding to a surface comprising guanidino moieties, or angiogenic materials to increase cell attachment

and/or thrombogenicity, which have nothing to do with stimulation of VEGF or growth factors.

Applicants have always consistently used the terms "stimulation compound" to mean a stimulation compound for producing VEGF or a growth factor. See page 4, lines 3-5, page 13, lines 19-26, and page 17, line 29 - page 18, line 4.

The Section 102 rejections must be withdrawn because nothing in the applied references discloses "stimulation compounds that stimulate production of VEGF" or "growth factor". The section 103 rejections must be withdrawn because there is no teaching or suggestion to stimulate VEGF or growth factor production.

Applicants expand on these points in the following remarks.

II. Rejections based on 35 U.S.C. §102

In the interest of brevity, Applicants incorporate by reference all arguments presented in the communication filed January 5, 2004 as if restated herein.

1. At page 2 of the Office Action, claims 31-35 are finally rejected under 35 U.S.C. §102 (b) as being anticipated by Carlyle, et al. (WO 99/37337).

The Examiner maintains that Carlyle, et al. teach a substrate on which is coated VEGF or related factors, which are attached via chemical bonding, crosslinking or an adhesive, and thus anticipates the claim subject matter.

Applicants respectfully traverse the rejection. Carlyle, et al. do not anticipate the present invention as set forth in claims 31-35. Applicants have pointed out that as clearly disclosed in the present invention, stimulating compounds are not growth factors, but compounds that stimulate the production of growth factors including VEGF. See the

specification at page 2, lines 26-27, page 4, lines 3-5, page 13, lines 19-26, and page 17, line29 - page 18, line 4.

The specific teaching and examples in Carlyle, et al. concentrate on the attachment of already isolated growth factors onto the substrates, while the subject matter of independent claim 31 is directed to the method of associating a biocompatible material with a stimulation compound to stimulate the growth of growth factors such as VEGF on a medical device, which in turn stimulates the growth of cells. This method is not specifically exemplified nor mentioned in Carlyle, et al. Thus, the subject matter of claim 31 is different from the teachings of Carlyle, et al.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102. Applicants respectfully submit that Carlyle, et al. do not teach every element of claim 31, and therefore fail to anticipate claim 31.

Dependent claims 32-35, which are dependent from independent claim 31, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Carlyle, et al. Applicants maintain for the reasons stated above, claims 32-35 likewise patentably distinguish over Carlyle, et al. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further

distinguish these claims from the cited references. Therefore, dependent claims 32-35 are also believed to be in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-35 under 35 U.S.C. §102 (b) as being anticipated by Carlyle, et al.

2. At page 3 of the Office Action, claims 31-33 are rejected under 35 U.S.C. §102 (b) as being anticipated by Keogh (U.S. Patent Number 6,033,719).

The Examiner notes that Keogh teaches a device on which is coated a biomolecule factor through covalent bonds and thus anticipates claims 31-33.

Applicants respectfully traverse the rejections.

Keogh appears to disclose improved methods for covalently attaching a biomolecule to a substrate surface, and specifically, to covalently immobilize at least one biomolecule on the surface of a biomaterial. See col. 2, lines 30-34. Keogh specifically teaches the selection of only biomolecules having a 1, 2 dicarbonyl moiety for covalently bonding to such biomaterial surfaces comprising guanidino moieties. See col. 3, lines 56-59; and col. 6, lines 22-56. Keogh does not teach a stimulation compound for stimulating the growth of growth factors. In addition, stimulation compounds do not necessarily have to comprise a 1, 2 dicarbonyl. Thus, the selection in Keogh from the broad range of biomolecules of ones fitting the criteria is related to a different invention than that disclosed in claim 31. Therefore Keogh does not anticipate the subject matter of claim 31.

Keogh does not disclose, teach or suggest a stimulation compound for stimulating the growth of growth factors. Keogh pertains only to biomolecules having a 1,2 dicarbonyl moiety for covalently bonding to biomaterial surfaces comprising

guanidino moieties for use in medical devices (col. 3, lines 57-60), and teaches away from providing anything else. Keogh refers even more specifically to providing guanidino moieties by amination of the biomaterials (col. 5, lines 11-32), followed by synthesis of guanidino moities (col. 4, lines 38-63), or by grafting of molecules (col. 5, lines 47-52), after which a resulting biomaterial surface comprising the guanidino moiety is covalently bonded to a biomolecule comprising a 1,2 dicarbonyl moiety, the covalent bonds immobilizing the biomolecule on the surface of a medical device to form a coating thereon (see abstract, col. 2, lines 30-45, claims 1, 11, 21, and 32) or to form a crosslinked coating thereon (see also claims 43, 53 and 65). Keogh is neither anticipatory nor suggestive of the present invention as set forth in any of Applicant's claims.

Claims 32-33, which are dependent from independent claim 1, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Keogh. Applicants maintain for the reasons stated above, claims 32-33 likewise patentably distinguish over Keogh. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 32-33 are also believed to be in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-33 under 35 U.S.C. §102 (b) as being anticipated by Keogh.

3. At page 3 of the Office Action, claims 1-2, 7, 23-24, 26, 28, 31-33, and 35 are finally rejected under 35 U.S.C. §102 (b) as being anticipated by Martin, et al. (WO 98/20027).

The Examiner contends that Martin et al. teach a device onto or into which a VEGF agonist is attached (see for examples the claims), and therefore anticipates claims 1-2, 7, 23-24, 26, 28, 31-33, and 35.

Applicants respectfully traverse the rejections.

Martin, et al. appears to teach a therapeutic use of growth factors, i.e. the inhibition of hyperplasia. See page 1, lines 4-6, page 4, lines 25-29 and page 5, lines 14-19 and 24-28. In addition, Martin, et al. appear to teach that VEGF agonists can be used in practicing their invention. See page 10, line 22 to page 13, line 17. The reference defines an agonist as a molecule which binds to a receptor to which VEGF normally binds, and has substantially the same effects as a VEGF would have. See page 10, lines 25-26. Thus, a VEGF agonist functions like a VEGF and takes the place of VEGF.

The present invention as set forth in claims 1 and 31 distinguishes over the Martin reference. Claims 1 and 31 are directed to a stimulation compound that stimulates the production of growth factors like VEGF. This is different than the teaching of Martin, et al., which is directed to use of VEGF or its agonists in suppressing intimal hyperplasia in situations where intimal hyperplasia arises when the endothelium is wholly or largely intact, and thus potentially capable of preventing or treating de novo stenosis (see Martin, et al. p. 4, lines 25-29). The Martin reference further states at page 38, lines 11-13, "it is unlikely that the inhibitory effect of arterial VEGF gene transfer on intimal thickening reported here is due to VEGF-stimulated re-endothelialization." The teachings of Martin, et al. regarding VEGF are inconsistent with Applicants' invention

set forth in independent claims 1 and 31. As such, Martin, et al. teach away from the present invention.

Martin, et al. teach a different invention, and fail to teach every element of the invention set forth in claims 1 and 31. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Martin, et al. is neither anticipatory nor suggestive of the present invention set forth in claims 1 and 31.

Claims 2, 7, 23-24, 26, 28, 32-33, and 35, which are dependent from independent claims 1 and 31, respectively, were also rejected under 35 U.S.C. §102(b) as being unpatentable over Martin, et al. Applicants maintain for the reasons stated above, claims 2, 7, 23, 24, 26, 28, 32-33 and 35 likewise patentably distinguish over Martin, et al. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2, 7, 23, 24, 26, 28, 32-33 and 35 are also believed to be in condition for allowance. Applicants respectfully request withdrawal of the rejection of claims 1-2, 7, 23-24, 26, 28, 31-33, and 35 under 35 U.S.C. §102 (b) as being anticipated by Martin, et al.

4. At page 3 of the Office Action, claims 31-33 are rejected under 35 U.S.C.§102 (a) as being anticipated by Slaikeu, et al. (WO 01/03607).

The Examiner notes that Slaikeu, et al. teach a medical device on which is coated or associated an angiogenic factor and thus anticipates claims 31-33.

Applicants respectfully traverse the rejections.

Slaikeu, et al. appear to disclose a stent coated with a composition having an angiogenic response. See page 7, lines 13-23. A long list of angiogenic materials including a growth factor, a nucleic acid, a pharmaceutically active compound and so on, is listed, as long as it produces the required angiogenic response. See page 11, line 8, to page 13, line 29. There is no teaching of how to associate a stimulation compound with a biocompatible material that stimulates the production of growth factors, the subject matter of claim 31. Slaikeu, et al. teach a different invention and do not anticipate claim 31 because they do not teach every element of the invention set forth in claim 31. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Slaikeu, et al. fail as a reference for sustaining a rejection based on 35 U.S.C. §102 (a).

Claims 32-33, which are dependent from independent claim 31, were also rejected under 35 U.S.C. §102(a) as being unpatentable over Slaikeu, et al. Applicants maintain for the reasons stated above, that dependent claims 32-33 likewise patentably distinguish over Slaikeu, et al. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Claims 32-33 are also believed to be in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 31-33 are rejected under 35 U.S.C. §102 (a) as being anticipated by Slaikeu, et al.

III. Rejections based on 35 U.S.C. § 103(a)

1. On page 4 of the Office Action, claims 1-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al.

The Examiner contends that Carlyle, et al. teach a needed medical device on to which VEGF has been attached to promote population of the device with viable cells and other positive results, and thus Carlyle, et al. teach all of the claimed devices in detail through the reference and also details means for attaching the peptide to the device in all the methods Applicants' claim. The Examiner also contends that Carlyle, et al. use VEGF, though does not teach using a VEGF stimulation compound, but adds that at the time the invention was made it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a VEGF stimulation compound for the VEGF used by Carlyle, et al. because Martin teaches that using such compounds produces like results to using the peptide itself, and therefore the references clearly provide a reasonable expectation of success that using known stimulator/agonist of VEGF on a medical device would produce the same desired results as sought by Carlyle et al. The Examiner further notes that as the references clearly indicate that the various proportions and amounts of the ingredients used in the claimed device are result effective variables, they would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references.

Applicants respectfully traverse the rejections.

Applicants have noted they agree with the Examiner that Carlyle, et al. use VEGF, but do not teach using a VEGF stimulation compound. However, as is clearly disclosed in the present invention, stimulating compounds are not growth factors, but compounds that stimulate the production of growth factors, including VEGF. See page 2, lines 26-27, page 4, lines 3-5, page 13, lines 19-26 and page 17, line 29 - page 18, line 4. Applicants make use of a stimulation compound that stimulates production of VEGF (or a growth factor), which in turn stimulates production of endothelial cells. The Carlyle and Martin references pertain only to the later production of endothelial cells, and not the stimulation of production of VEGF (or growth factor). Applicants' invention is concerned with the former stimulation, i.e., of production of VEGF.

Carlyle, et al. teach the association of growth factors with substrates to stimulate cell growth. The specific teaching and examples in Carlyle, et al. concentrate on the attachment of isolated growth factors onto the substrates, as noted above. Further, Applicants maintain as noted hereinabove that Carlyle, et al. teach away from the present invention as claimed.

Martin, et al. appear to teach the inhibition of hyperplasia, and disclose therapeutic use of growth factors, to suppress intimal hyperplasia in situations where intimal hyperplasia arises when the endothelium is wholly or largely intact, and thus potentially capable of preventing or treating de novo stenosis. See page 1, lines 4-6, page 4, lines 25-29, and page 5, lines 14-19, and 24-28. In addition, Martin, et al. teach that VEGF agonists can be used in practicing their invention, and that a VEGF agonist functions like a VEGF and takes the place of VEGF. See page 10, line 22 to page 13, line 17. While Carlyle, et. al. teach that growth factors can promote cell growth, Martin,

et al. find that VEGF and its agonists can suppress or treat de novo stenosis, another use for VEGF. Martin, et al. also do not teach bioprosthetic material lacking endothelium. Further, Martin, et al. (as noted hereinabove) teach away from the present invention. Martin, et al. state at page 38, lines 11-13, "it is unlikely that the inhibitory effect of arterial VEGF gene transfer on intimal thickening reported here is due to VEGF-stimulated re-endothelialization." The teachings of Martin, et al. regarding VEGF are inconsistent with Applicants' invention set forth in the claims.

The cited combination must be considered for its antithetical teachings. One of ordinary skill in the art would be led by the cited combination in a direction divergent from the path Applicants have taken. Thus, there is no motivation to combine the teaching of Carlyle, et. al. with that of Martin, et al. In addition, even if combined, the combination fails to meet the present invention as claimed. The combination of references teaches VEGF and not stimulation compounds, as set forth in independent claims 1 and 31.

Three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. MPEP § 2142. Applicants respectfully traverse the rejection since the prior art fails to disclose all the claim limitations and there would be no motivation to combine the references as proposed by the Examiner, since the combined teaching does not teach or motivate stimulation compounds.

Dependent claims 2-30 and 32-35, which are dependent from independent claims 1 and 31, were also rejected under 35 U.S.C. §103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al. Applicants maintain for the reasons stated above, claims 2-30 and 32-35 likewise patentably distinguish over Carlyle, et al. and Martin, et al. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 2-30 and 32-35 are also believed to be in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 1-35 under 35 U.S.C. § 103(a) as being anticipated by Carlyle, et al. in view of Martin, et al.

2. On page 5 of the Office Action, claims 3-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. (U.S. Patent Number 6,124,131) or Tsuzuki, et al. (Cancer Research. 60.2000).

The Examiner contends that neither Carlyle, et al. nor Martin, et al. specifically teach using HIF-lα as the stimulator/agonist of VEGF, but that it would have been obvious at the time the invention was made to use HIF-lα as the agonist as taught by Martin in the process of Carlyle because Semenza and Tsuzuki teach that HIF-lα is a known agonist of VEGF. The Examiner asserts that there was a reasonable expectation that substituting HIF-lα for the VEGF in the invention of Carlyle would produce like results. Accordingly, the Examiner contends that the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

Applicants respectfully traverse the rejections.

Applicants agree with the Examiner that neither Carlyle, et al. nor Martin, et al. specifically teach using HIF-Iα as the stimulator of VEGF, and that both Semenza and Tsuzuki, et al. teach that HIF-Iα is a known agonist of VEGF. However, as noted in Martin, et al., a VEGF agonist functions like a VEGF and takes the place of VEGF. Thus, an agonist is not a stimulation compound that stimulates the growth of VEGF, but only a VEGF look alike.

Further, Semenza teaches the discovery and isolation of unique variant forms of HIF-1α polypeptide that are stable under hypoxic and nonhypoxic conditions. See col. 2, lines 63-65. HIF-Iα polypeptide, when dimerized with HIF-1β, is a DNA binding protein, which is characterized as activating structural gene expression where the promoter region of the structural gene contains a HIF-1 binding site. See col. 5, lines 6-13. Examples of structural genes include erythropoietin (EPO), vascular endothelial growth hormone (VEGF) and glycolytic genes. See col. 5, lines 13-15. The HIF-Iα polypeptides can also be used to produce antibodies which are immunoreactive or selectively bind to epitopes of the sHIF-Iα polypeptides. An antibody which "selectively binds" to sHIF-Iα is an antibody that binds sHIF-Iα with a higher affinity the antibody binds to wild-type HIF-Iα. See col. 13, lines 25-30.

At the same time, Tsuzuki, et al. attempt to quantify the tumor activation of VEGF promoter in host stromal cells by implanting VEGF and wild-type embryonic stem cells in mice. See abstract. They teach that HIF-Iα binds to HRE of a target gene such as VEGF. See page 6248, col.1, Introduction. VEGF proteins bind to VEGF receptors on endothelial cells to mediate physiological function. See page 6248, col. 2, Introduction.

While Carlyle, et al. teach that growth factors can promote cell growth, Martin et al. find that VEGF and its agonists can also suppress or treat de novo stenosis. Semenza teaches the discovery and isolation of unique variant forms of HIF-1α. Tsuzuki, et al. attempt to quantify the activation of VEGF promoter by implanting VEGF and stem cells in mice. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Carlyle, et al. in view of Martin, et al. with Semenza or Tsuzuki, et al. to arrive at a medical device, such as an implantable medical device, a catheter, a dressing or a surgical instrument, having stimulation compounds that stimulates the production of VEGF, the subject matter of claim 1, as proposed by the Examiner. "(O)bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Bond*, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990)(quoting *Carella v. Starlight Archery and Pro Line Co.*, 231 USPQ 644, 647 (Fed. Cir. 1986)). "[T]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989) (quoting *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

In addition, the Examiner's suggestion of reasonable expectation of success is also untenable since there is no motivation to combine the references. The three criteria to establish a *prima facie* case of obviousness, i.e. (1) that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (2) that there must be a reasonable expectation of success; and (3) that the prior art reference,

or combination of references, must teach or suggest all the claim limitations, are not met. MPEP § 2142.

Therefore, claim 1 is not obvious over Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. or Tsuzuki, et al.

Claims 3-7, which are dependent from independent claim 1, were rejected under 35 U.S.C. §103(a) as being unpatentable over Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. (U.S. Patent Number 6,124,131) or Tsuzuki, et al. (Cancer Research. 60.2000). Applicants maintain for the reasons stated above with regard to independent claim 1, claims 3-7 likewise patentably distinguish over Carlyle, et al., Martin, et al., and Semenza, et al. or Tsuzuki et al. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, dependent claims 3-7 are also believed to be in condition for allowance.

Applicants respectfully request withdrawal of the rejection of claims 3-7 under 35 U.S.C. § 103(a) as being anticipated by Carlyle, et al. in view of Martin, et al. and further in view of Semenza, et al. or Tsuzuki, et al.

III. Conclusion

In view of the foregoing arguments, it is believed that all pending claims are in condition for allowance. Applicants respectfully request favorable reconsideration and early allowance of all pending claims 1-35.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' attorney of record, Hallie A. Finucane at (952) 253-4134.

Respectfully submitted,

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